

**Domino Michael/Michael reaction catalyzed by switchable modularly designed organocatalysts**

Journal:	<i>Organic & Biomolecular Chemistry</i>
Manuscript ID	OB-ART-10-2021-001991.R1
Article Type:	Paper
Date Submitted by the Author:	12-Nov-2021
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ARTICLE

Domino Michael/Michael reaction catalyzed by switchable modularly designed organocatalysts

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Received 00th January 20xx,
Accepted 00th January 20xx

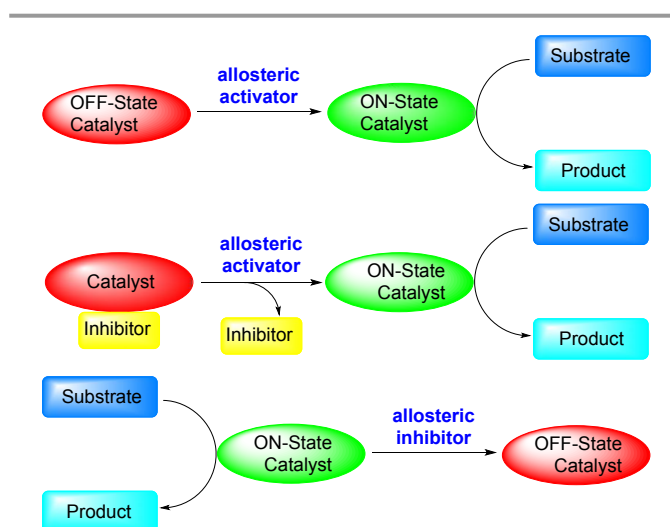
DOI: 10.1039/x0xx00000x

The domino Michael/Michael reaction between (*E*)-7-aryl-7-oxohept-5-enals and *trans*-cinnamaldehydes was investigated by using the modularly designed organocatalysts (MDOs). It was found that both the enamine and iminium catalytic modes of the MDOs are switchable and can be individually switched on and off by using appropriate combinations of the precatalyst modules and the reaction reconditions. When both the enamine and iminium catalysis modes of the MDOs are switched on, the desired domino reaction products can be obtained in good yields and stereoselectivities under optimized conditions.

Introduction

In a living cell, numerous reactions occur simultaneously. To ensure that all these reactions are not interfering with each other, these reactions must proceed with exact spatial and temporal control.¹ To achieve that, the enzymes that catalyze these reactions are often regulated by feedback loops or triggers, which means their catalytic activities must be switchable and the switching must be reversible.¹ The regulation of an enzyme by binding an effector molecule at a site other than the enzyme's active site is known as an allosteric regulation, which can be either an allosteric activation or an allosteric inhibition.² Simple chemical systems that mimic enzyme reactivities have been actively pursued by chemists in the past decades with the goals of understanding the fundamental questions regarding enzyme activation and developing synthetically useful catalysts inspired by the enzymes. As a result of these efforts, many switchable catalytic systems based on the allosteric activation mode have been reported.³ Light, small molecules, pH (H⁺), temperature, and ions/metals have been used as the allosteric activation effectors. Scheme 1 below shows how allosteric regulation works in general. The off-state catalyst may be directly turned on by the allosteric activator, which then catalyzes the desired reaction (Scheme 1, top figure). Alternatively, the catalyst may be first turned off by an inhibitor, and then turned on through the removal of the inhibitor by the activator (Scheme 1, middle figure).⁴ Of course, switchable catalytic systems can also be designed based on the allosteric inhibition mode, in which the catalysis of the catalyst can be turned off by an allosteric inhibitor (Scheme 1, bottom figure).⁵

Since List and Barbas reported the first example of a proline-catalyzed intermolecular aldol reaction in 2000,⁶ many proline



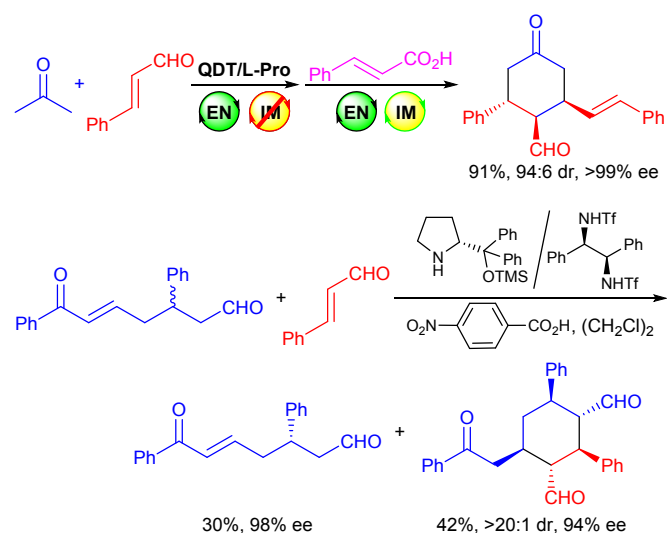
Scheme 1. Reported allosteric regulations of switchable catalysts via an allosteric activator or an allosteric inhibitor.

derivatives have been developed in the last two decades as organocatalysts to achieve a plethora of stereoselective transformations.⁷ Nonetheless, the allosteric regulations of the enamine or iminium catalysis of an amine catalyst is seldom studied in the past. To our knowledge, only Leigh and Leung have reported achiral rotaxane-based acyclic secondary amine catalyst, in which both the enamine and iminium catalysis can be subjected to allosteric inhibition simultaneously by proton⁸ due to the conformational change of the catalyst after protonation.⁸

Most recently, we reported that modularly designed organocatalysts (MDOs),⁹ which form in the reaction media via the self-assembly of cinchona alkaloid derivatives (such as QDT) and amino acids (such as L-Pro), are switchable catalysts.^{9f} The iminium catalysis mode of the MDOs that is inhibited by the cinchona alkaloid module (i.e., QDT) can be switched on by adding an appropriate acid and, upon the switch-on, these

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x



Scheme 2. Some reported examples related to the current study.

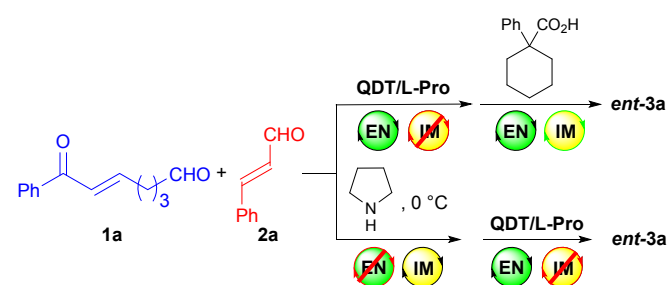
MDOs can be used for catalyzing a diastereodivergent^{9g} domino Mannich condensation/Michael/Michael reaction¹⁰ between ketones and *trans*-cinnamaldehydes (Scheme 2, top equation).^{9f}

On the other hand, despite the advances in organocatalysis, the organocatalytic asymmetric Michael addition of ketones or aldehydes to α,β -unsaturated aldehydes via the enamine/iminium catalysis remains a challenging task,^{9f,11-12} and only a few examples are available.^{9f,11} In this respect, Xu and coworkers have reported a kinetic resolution of racemic enals via an organocatalyzed asymmetric domino Michael/Michael reaction with cinnamaldehydes using a combination of the Jørgensen-Hayashi catalyst and a diamine-derived cocatalyst, involving both the enamine and iminium activations of the catalyst (Scheme 2, bottom equation).^{11b} Hong and coworkers have also reported a domino Michael/Michael/aldol condensation reaction between enals and enals.^{11c} Inspired by these results, we studied the domino Michael/Michael reaction of achiral enals **1**, with which we have developed many useful synthetic methods,⁹ with *trans*-cinnamaldehydes using our switchable MDOs as the catalyst, and discovered that both the enamine and iminium catalytic modes can be individually switched on and off if appropriate combinations of precatalyst modules and/or reaction conditions are employed. Herein we wish to report the details of our findings.

Results and discussion

The achiral enonal compound **1a** and cinnamaldehyde (**2a**) were adopted as the substrates for the stereoselective synthesis of cyclohexanedial **ent-3a** (Table 1), since, as in Xu's case,^{11b} the domino Michael/Michael reaction between **1a** and **2a** requires both enamine and iminium catalysis. First, we conducted some experiments to determine whether an acid is indeed needed to switch on the iminium catalysis of the MDO. As the results in Table 1 show. When the MDO of **4a/5a** (QDT/L-Pro, Scheme 4) was applied together with the acid **6a** at room temperature, the

desired 1,3-cyclohexanedial **ent-3a** was obtained in 53% yield, 80:20 dr, and 58% ee after 24 h, suggesting both the enamine and iminium catalysis was working under these conditions



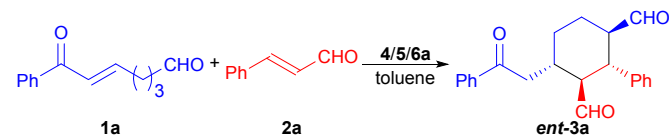
Scheme 3. Switching on and off the iminium and enamine catalytic modes

(entry 1). In contrast, the control reaction without adding any acid gave only trace amount of product under otherwise identical conditions (entry 2). These results confirm that the presence of an acid is crucial for the success of this domino Michael/Michael reaction. Further control reactions also revealed that the combination of **4a** (QDT) and **6a** (entry 3), and **5a** (L-Pro) and **6a** (entry 4) failed to catalyze the reaction. Similarly, the individual modules **4a** (entry 5) and **5a** (entry 6), and the acid **6a** (entry 7) also failed to catalyze the reaction. Similar results were also obtained with the MDO of **4b/5a** (entries 8-14), except that a better product yield (77%), dr (89:11), and ee value (78%) were obtained with this MDO in the presence of the acid **6a** (entry 8). Since we have demonstrated that MDOs (such as **4a/5a**) is able to catalyze enamine-mediated reaction without any acid,⁹ the failure of these MDOs to catalyze the domino Michael/Michael reaction without an acid (entries 2 and 9) is most likely because the iminium catalysis mode of these catalysts is not working without an acid cocatalyst.^{9f} The above results again show that inhibited iminium catalysis can be switched on by adding the acid cocatalyst (Scheme 3, upper equation).^{9f}

Pyrrolidine (**5c**) is a good catalyst for both enamine and iminium catalysis. To further establish that the reaction indeed goes via the enamine and iminium catalysis,¹² we tried the reaction with **5c** as the catalyst, and the desired racemic product **3a** was obtained in 69% yield and 95:5 dr (entry 15). The use of **5c** together with **4a** (QDT) did not show any improvement in terms of product yield and stereoselectivities (entry 16). These results exclude a possible involvement of the enolate mechanism in this reaction, because, if an enolate mechanism is responsible for the observed formation of **3a**, adding QDT should have facilitated the domino reaction since QDT is a stronger base than **5c**. It is surprising that when these reactions were repeated at 0 °C with **5c** or **4a/5c** as the catalyst, no desired domino reaction was observed (entries 17-18). These surprising failures may be due to the switch-off of the enamine, the iminium, or both the enamine and iminium catalysis modes by this lower temperature. To find out what is actually switched off by the lower temperature, we conducted some additional control reactions. It was found that, while the combination of **5a** (L-Pro) and **5c** catalyzes the reaction at rt (entry 19), it also failed at 0 °C (entry 20). Only when **4a** (QDT), **5a** (L-Pro), and **5c** were used

together, the desired domino reaction would proceed again at 0 °C (entry 22). We have shown above that MDO of **4a/5a** can't catalyze the iminium catalysis, but it is known to catalyze the enamine-mediated reactions.⁹ Thus, it can be concluded that

Table 1 Switching on and off of the iminium and/or enamine catalysis in the domino Michael/Michael reaction of **1a** and **2a**^a

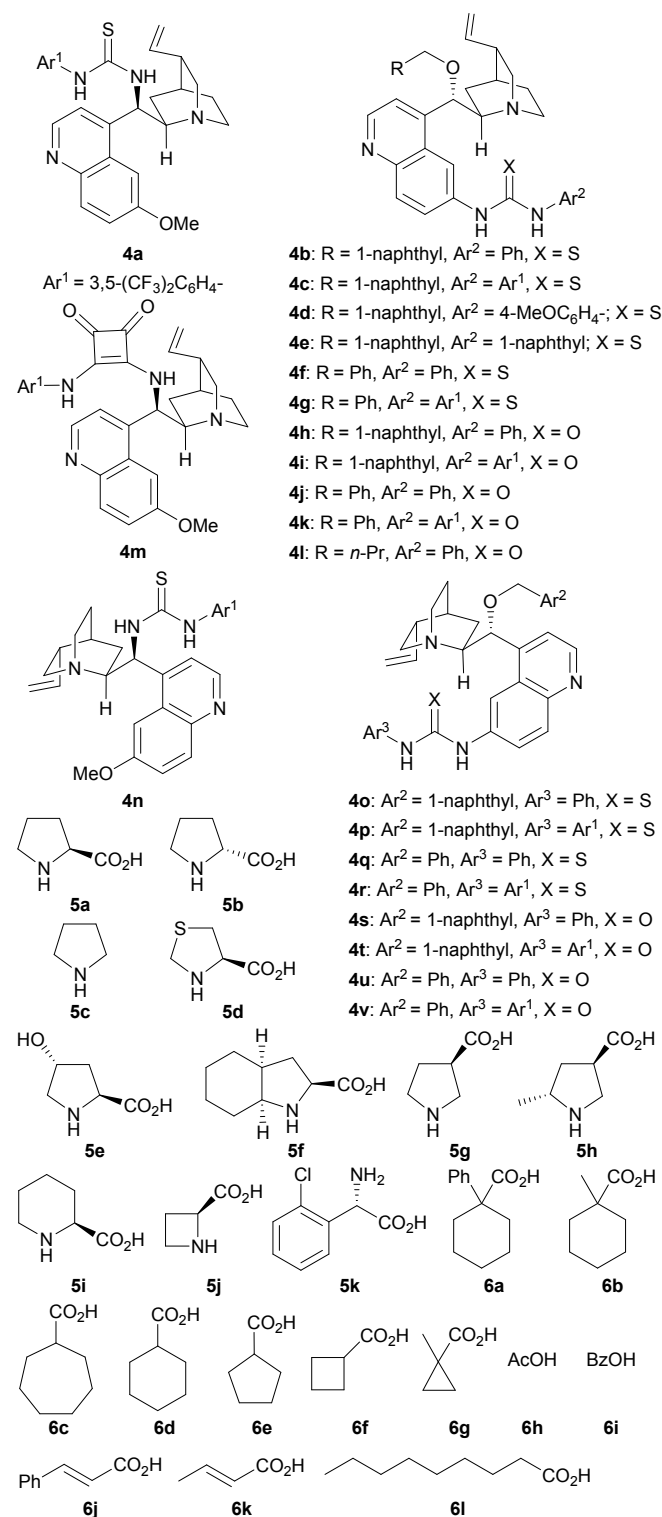


Entry	Precatalyst Modules	Acid	Yield (%) ^b	dr ^c	ee (%) ^d	
1	4a	5a	6a	53	80:20	58
2	4a	5a	---	trace	---	---
3	4a	---	6a	NR ^e		
4	---	5a	6a	NR ^e		
5	4a	---	---	NR ^e		
6	---	5a	---	NR ^e		
7	---	---	6a	NR ^e		
8	4b	5a	6a	77	89:11	78
9	4b	5a	---	trace	---	---
10	4b	---	6a	NR ^e		
11	---	5a	6a	NR ^e		
12	4b	---	---	NR ^e		
13	---	5a	---	NR ^e		
14	---	---	6a	NR ^e		
15	---	5c	---	69	95:5	0
16	4a	5c	---	57	93:7	2
17 ^f	---	5c	---	NR ^e		
18 ^f	4a	5c	---	trace	---	---
19	---	5a+5c	---	68	92:8	3
20 ^f	---	5a+5c	---	trace	---	---
21	4a	5a+5c	---	85	99:1	14
22 ^f	4a	5a+5c	---	65	83:17	17

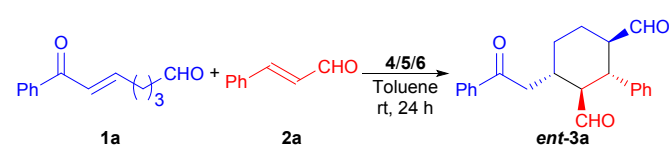
^aUnless otherwise specified, all reactions were carried out with **1a** (0.12 mmol), **2a** (0.10 mmol), the precatalyst modules (**4a**, **5a**, and/or **5c**, 0.010 mmol each, 10 mol%), and the acid cocatalyst **6a** (0.010 mmol, 10 mol%) in dry toluene (1.0 mL) at room temperature. ^bYield of the isolated major diastereomeric product after column chromatography. ^cDetermined by ¹H NMR analysis of the crude product. ^dDetermined by HPLC analysis on a ChiralPak IC column. ^eNo reaction. ^fCarried out at 0 °C.

the iminium catalysis mode of **5c** must still work at 0 °C; otherwise, we should not be able to obtain any product with **4a/5a/5c** at this temperature (entry 22). Thus, what actually is switched off at 0 °C must be the enamine catalysis mode of **5c**. In summary, we have showed that the enamine catalysis mode of pyrrolidine (**5c**) can be switched off by a lower temperature of 0 °C. With this interesting property of **5c**, we can build a ternary system (such as **4a/5a/5c**) at 0 °C, in which pyrrolidine (**5c**) is responsible for the iminium catalysis only and the MDO (such as **4a/5a**) is responsible for the enamine catalysis only (Scheme 3, lower equation). Nevertheless, since this ternary system leads to a poor enantioselectivity for the desired domino product (entries 21 and 22), we focused on the first approach (the switch-on by an acid cocatalyst) in our further optimizations.

While the MDOs **4a/5a** and **4b/5a** both yield the desired domino Michael product **ent-3a** in the presence of acid **6a** (Table 2, entries 1 and 2), the latter gives higher product yield and stereoselectivities (entry 2). Therefore, precatalyst module **4b** was selected for the screening of the other amino acid precatalyst modules **5** (Scheme 4). As the results in Table 2 show, except for **5g** (entry 7), which gave a much lower ee value of the product **ent-3a** than **5a** did (entry 2), all the other amino acid precatalysts are not reactive at all (entries 3-6, 8-11). Since



Scheme 4. Structure of the catalyst modules and acids used in this study.

Table 2. Catalyst screening^a

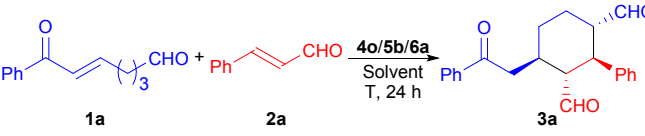
Entry	Modules/Acid	Yield (%) ^b	dr ^c	ee (%) ^d
1	4a 5a 6a	53	80:20	58
2	4b 5a 6a	77	89:11	78
3	4b 5b 6a	trace	---	---
4	4b 5d 6a	trace	---	---
5	4b 5e 6a	trace	---	---
6	4b 5f 6a	trace	---	---
7	4b 5g 6a	81	93:7	9
8	4b 5h 6a	trace	---	---
9	4b 5i 6a	0	---	---
10	4b 5j 6a	0	---	---
11	4b 5k 6a	0	---	---
12	4c 5a 6a	84	96:4	61
13	4d 5a 6a	trace	---	---
14	4e 5a 6a	66	87:13	68
15	4f 5a 6a	78	89:11	77
16	4g 5a 6a	70	84:16	69
17	4h 5a 6a	79	96:4	63
18	4i 5a 6a	80	94:6	68
19	4j 5a 6a	76	93:7	63
20	4k 5a 6a	50	70:30	68
21	4l 5a 6a	87	94:6	73
22	4m 5a 6a	70	83:17	35
23	4n 5a 6a	0	---	---
24	4n 5b 6a	56	82:18	55 ^e
25	4o 5b 6a	89	95:5	78^e
26	4p 5b 6a	85	94:6	72 ^e
27	4q 5b 6a	88	98:2	77 ^e
28	4r 5b 6a	83	94:6	73 ^e
29	4s 5b 6a	33	86:14	65 ^e
30	4t 5b 6a	27	71:29	65 ^e
31	4u 5b 6a	35	88:12	70 ^e
32	4v 5b 6a	66	72:28	39 ^e
33	4o 5b 6b	63	75:25	62 ^e
34	4o 5b 6c	62	83:17	75 ^e
35	4o 5b 6d	65	80:20	71 ^e
36	4o 5b 6e	72	93:7	74 ^e
37	4o 5b 6f	76	90:10	77 ^e
38	4o 5b 6g	57	71:29	70 ^e
39	4o 5b 6h	trace	---	---
40	4o 5b 6i	63	93:7	78 ^e
41	4o 5b 6j	60	60:40	75 ^e
42	4o 5b 6k	60	88:12	78 ^e
43	4o 5b 6l	73	90:10	73 ^e

^aAll reactions were carried out with **1a** (0.12 mmol), **2a** (0.10 mmol), the precatalyst modules **4** and **5** (0.010 mmol each, 10 mol%), and the acid cocatalyst **6** (0.010 mmol, 10 mol%) in dry toluene (1.0 mL) at room temperature for 24 h.

^bYield of the isolated major diastereomeric product after flash column chromatography. ^cDetermined by ¹H NMR analysis of the crude reaction product.

^dDetermined by HPLC analysis on a ChiralPak IC column. ^eThe opposite enantiomer was obtained as the major product.

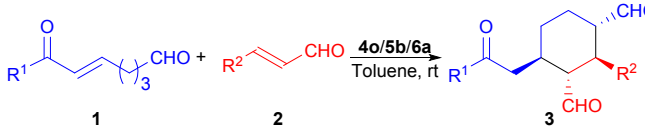
5a gave the best product ee values (entry 2), it was chosen for the screening the cinchona alkaloid-derived precatalyst modules **4** (Scheme 4). For quinidine-derived 6'-thioureas (**4c-4g**), they all led to the formation of the desired product in quite similar yields and stereoselectivities (entries 12, 14-16), except for the module **4d** (entry 13), which gave only trace amount of

Table 3. Optimization of the reaction conditions^a


Entry	Solvent	Yield (%) ^b	dr ^c	ee (%) ^d
1	Toluene	89	95:5	78
2	Benzene	73	86:14	79
3	Xylene	trace	---	---
4	C ₆ H ₅ Cl	50	72:28	76
5	C ₆ H ₅ CF ₃	trace	---	---
6	THF	<5	---	---
7	<i>c</i> -C ₅ H ₉ OMe	trace	---	---
8	CH ₂ Cl ₂	65	81:19	60
9	CHCl ₃	75	90:10	76
10	ClCH ₂ CH ₂ Cl	71	88:12	68
11	MeOH	63	96:4	30
12	MeCN	85	97:3	51
13	DMSO	67	83:27	56
14	Toluene	40	61:39	84 ^e

^aUnless otherwise indicated, all reactions were carried out with **1a** (0.12 mmol), **2a** (0.10 mmol), the precatalyst modules **4o** and **5b** (0.010 mmol each, 10 mol%), and the acid cocatalyst **6a** (0.010 mmol, 10 mol%) in the specified dry solvent (1.0 mL) at room temperature for 24 h. ^bYield of the isolated major diastereomeric product after flash column chromatography. ^cDetermined by ¹H NMR analysis of the crude reaction product. ^dDetermined by HPLC analysis on a ChiralPak IC column. ^eThe reaction was performed at 0 °C.

product. Similar results were also obtained by using the quinidine-derived 6'-ureas (**4h-4l**, entries 17-21). While some of these modules (such as **4c**, **4h**, **4j**, and **4l**) produces slightly better diastereoselectivities than that of **4b**, the ee values obtained are usually lower. In contrast, quinidine-derived squaramide **4m** (entry 22) gave a much lower ee value of the product than QDT (**4a**) and the 6'-thiourea **4b** do. Next, quinine-derived thiourea (**4n**, QNT) and 6'-(thio)ureas were screened as the modules. It was found that when QNT (**4n**) was used together with **5a** as the MDO, no desired product was obtained (entry 23). In contrast, when QNT (**4n**) was used together with D-Pro (**5b**) to form the MDO, the desired product was obtained in a decent yield and good stereoselectivities (entry 24). Comparing these results with those in entries 2 and 3, it is clear that there is a strong match-mismatch between the amino acid module and the cinchona alkaloid module^{9a} in this reaction: L-Pro (**5a**) matches with quinidine derivatives, while D-pro (**5b**) matches with quinine derivatives.^{9a} Because of this match-mismatch effect, the diastereodivergent catalysis⁹ we normally observed with the MDO-catalysis is not possible. Further screening revealed that the MDO of **4o/5b**, which is the pseudo-enantiomer of **4b/5a**, yielded the highest yield and stereoselectivities of the desired domino product (entry 25). The other quinine-derived 6'-thiourea modules (**4p-4r**) or 6'-urea modules (**4s-4v**) all yielded worse stereoselectivities (entries 26-32). It should be pointed out that the opposite enantiomer (i.e., **3a**) was obtained as the major product when **5b** (D-Pro) was used as the amino acid module and, therefore,

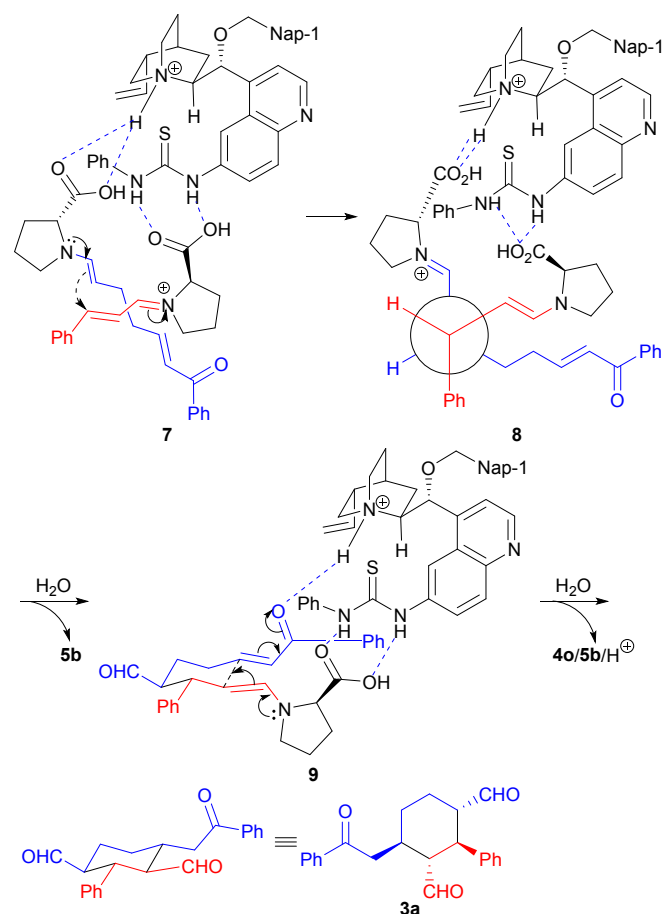
Table 4. Substrate scope study^a


Entry	R ¹	R ²	Time (h)	3 /Yield (%) ^b	dr ^c	ee (%) ^d
1	Ph	Ph	24	3a /89	95:5	78
2	Ph	4-MeOC ₆ H ₄	72	3b /50	84:16	45
3	Ph	4-MeC ₆ H ₄	48	3c /76	90:10	61
4	Ph	4-FC ₆ H ₄	48	3d /70	90:10	79
5	Ph	4-ClC ₆ H ₄	48	3e /65	84:16	67
6	Ph	4-BrC ₆ H ₄	48	3f /72	88:12	62
7	Ph	4-CNC ₆ H ₄	72	3g /56	80:20	76
8	Ph	Me	48	0 ^e	---	---
9	4-MeOC ₆ H ₄	Ph	48	3h /68	92:8	80
10	4-MeC ₆ H ₄	Ph	48	3i /72	92:8	66
11	4-FC ₆ H ₄	Ph	48	3j /68	88:12	72
12	4-ClC ₆ H ₄	Ph	48	3k /70	91:9	76
13	4-BrC ₆ H ₄	Ph	48	3l /61	80:20	77
14	3-BrC ₆ H ₄	Ph	48	3m /68	92:8	72
15	2-BrC ₆ H ₄	Ph	48	trace	---	---

^aAll reactions were carried out with **1** (0.12 mmol), **2** (0.10 mmol), the precatalyst modules **4o** and **5b** (0.010 mmol each, 10 mol%), and the acid cocatalyst **6a** (0.010 mmol, 10 mol%) in dry toluene solvent (1.0 mL) at room temperature for 24 h. ^bYield of the isolated major diastereomeric product after flash column chromatography. ^cDetermined by ¹H NMR analysis of the crude reaction product. ^dDetermined by HPLC analysis. ^eA complex mixture was obtained.

the product absolute stereochemistry is completely determined the amino acid module. Next, the acid cocatalyst (Scheme 4) was screened, and it turned out that worse results than that of **6a** in terms of both the product yields and stereoselectivities were obtained for all of the other cycloalkane carboxylic acids (**6b-6g**), acetic acid (**6h**), benzoic acid (**6i**), *trans*-cinnamic acid (**6j**), crotonic acid (**6k**), and nonanoic acid (**6l**) (entries 33-42 vs. entry 25).

The solvent used in this reaction was then optimized using the best catalyst system **4o/5b/6a**. As the results in Table 3 show, all the other organic solvents we screened are inferior to toluene in terms of the product yield and/or stereoselectivities (entries 2-13). Among these solvents, xylene (entry 3), trifluoromethylbenzene (entry 5), and ethereal solvents, such as THF (entry 6) and cyclopentenyl methyl ether (entry 7), are especially poor, since no desired product could be isolated from the reactions conducted in them. Finally, the reaction was carried out in toluene at 0 °C (entry 14). Although a slightly higher ee value of the product was obtained (84% ee), the yield and diastereoselectivity of this reaction dropped significantly. Once the reaction conditions were fully optimized, the scope of this reaction was probed. As the results in Table 4 show, besides *trans*-cinnamaldehyde (**2a**, entry 1), cinnamaldehydes with a substituent on the phenyl ring are also good substrates for this reaction (entries 2-7). While most of the substituted cinnamaldehydes gave very similar product ee values, 4-methoxy-substituted cinnamaldehyde gave a much lower ee value of the product (entry 2); however, no trend was observed

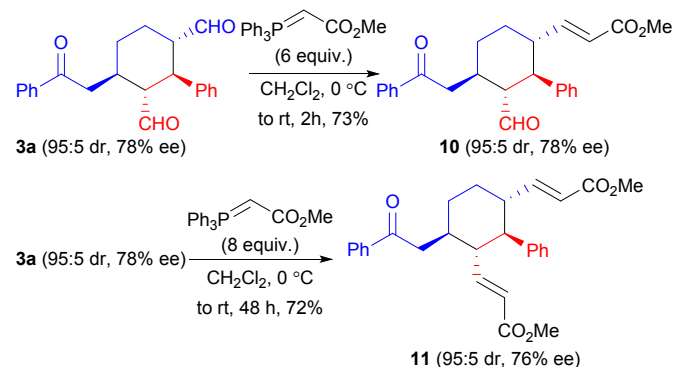


Scheme 5. Proposed favored transition states for the formations of product **3a**.

for the electronic effects of the substituents on the yields and stereoselectivities of this reaction. In contrast, the use of *trans*-crotonaldehyde in this reaction led to the formation of a complex reaction mixture (entry 8). On the other hand, enonals with a substituent on the *para* position of the phenyl ring are all good substrates for this reaction, and the electronic effects of these substituents have minimal influence on the product yields and stereoselectivities (entries 9–13). When the same substituent (i.e., bromo) was placed instead in the *meta* position of the phenyl ring, there was almost no change in the product yields and ee values (entry 14 vs. entry 13), although the diastereoselectivity observed was slightly better for the *meta*-substituted substrate. Nonetheless, when this substituent was placed in the *ortho*-position, only trace amount of the desired product was formed (entry 15). This negative result most likely was due to the steric effects of the *ortho*-bromo substituent.

The relative stereochemistry of the reaction product was determined by COSY experiments and the coupling constants using compound **3l** (For details, please see the SI). Since we could not grow a single crystal from the reaction products or their derivatives, the absolute stereochemistry of the reaction product was determined by comparing the major enantiomer obtained in our reaction and the major enantiomer obtained by using the Xu's catalytic system^{11b} (For details, please see the SI). Based on the reported computational study of the MDO

catalysis¹³ and our previous reported results,⁹ the following transition states were proposed to explain the stereochemical outcome of this reaction (Scheme 5). As shown



Scheme 6. Derivatization of the reaction product **3a**.

in transition state **7**, the enamine intermediate formed from **1a** and D-Pro (**5b**) and the iminium intermediate formed from **2a** and D-Pro (**5b**) self-assembled with the 6'-thiourea **4o** through hydrogen bonds between the carboxylic acid group of the D-Pro moieties and the ammonium as well as the thiourea moieties of **4o**. The attack of the (*E*)-enamine onto the *Re* face of α,β -unsaturated iminium intermediate from the back is favored, which leads to the formation of the intermediate with an (*S,S*)-stereochemistry for the two newly formed stereogenic centers (Please see structure **8**). After the hydrolytic removal of one of the D-Pro moieties, the intermediate adopts a chair conformation and reassembles with **4o**, with a new hydrogen bond being formed between the keto group of the enone and the ammonium of **4o** (transition state **9**). An intramolecular Michael addition of the enamine onto the enone moiety yields the expected product **3a** after a hydrolytic removal of the protonated MDO (**4o/5b/H⁺**).

Finally, some synthetic maneuvers were conducted to demonstrate the utility of the products. As shown in Scheme 6, selective reactions of the two aldehyde groups in compound **3a** with methyl (triphenylphosphoranylidene)acetate can be achieved: By using appropriate the loadings of the latter reagent, compounds **10** or **11** can be obtained with complete retention of the stereochemistry.

Conclusions

In summary, we have demonstrated that the enamine catalysis mode of the pyrrolidine can be switched on or off by temperature, while the iminium catalysis mode of the modularly designed organocatalysts (MDOs), which is switched off by the cinchona module, can be switched on by an acid cocatalyst. Based on these properties, we have developed two catalytic systems for the simultaneous enamine and iminium activations: a ternary system containing the MDO and pyrrolidine and a binary MDO system plus an acid cocatalyst. With the more selective binary system, we have achieved good yields and stereoselectivities in the domino Michael/Michael

reaction between (*E*)-7-aryl-7-oxohept-5-enals and *trans*-cinnamaldehydes under the optimized conditions.

Experimental

General Information

All reactions were conducted in 17 × 60 mm glass vials and monitored by TLC on silica gel plates (200 μm) and visualized by UV. Column chromatography was performed on silica gel (32–63 μm). ¹H NMR spectra was recorded on a 500 MHz or a 300 MHz spectrometer (126 MHz or 75 MHz for ¹³C NMR). Infrared spectra were measured on a Bruker Vector 22 instrument. Enantiomeric excesses (ee) were determined by chiral HPLC analysis using a Shimadzu instrument. ChiralPak IC, ID, columns (4.6 mm × 250 mm) were purchased from Daicel Chemical Industries. HRMS were conducted by the RCMI Core Facilities, Department of Chemistry, UTSA. All starting materials used in this study are known compounds and were either commercially available or synthesized according to the literature procedures.¹⁴ All of the precatalyst modules, except for **4d**, **4e**, **4f**, **4h**, **4j**, **4l**, **4o**, **4q**, **4s**, **4t**, and **4u**, are known compounds, and were either commercially available or synthesized according to the reported procedures.¹⁵ Those new modules were similarly synthesized from the corresponding cinchona-derived amines by reacting with the desired isocyanates or isothiocyanates.¹⁴ All the reagents were purchased from commercial sources and used as received. Solvents were dried according to standard protocols prior to use.

Experimental Procedures

General procedure for the synthesis of 3: A mixture of **4o** (5.8 mg, 0.010 mmol, 10 mol %) and **5b** (1.2 mg, 0.010 mmol, 10 mol %) in freshly distilled toluene (1.0 mL) was stirred for 15 min. at rt. Then the enonal **1** (24.2 mg, 0.12 mmol) and the enal **2** (13.2 mg, 0.1 mmol) were added one by one and the mixture was further stirred for another 5 min. at rt. Next, 1-phenylcyclohexanecarboxylic acid (**6a**, 2.0 mg, 0.010 mmol, 10 mol %) was added and the stirring was continued at rt for 24 h to 72 h (Table 4). After the completion of the reaction (monitored by TLC), the solvent was evaporated in a rotavapor under reduced pressure and the crude product obtained was purified by flash column chromatography using 70:30 hexane/EtOAc to give product **3a-m**.

Synthesis of Methyl (*E*)-3-[(1*R*,2*R*,3*R*,4*R*)-3-formyl-4-(2-oxo-2-phenylethyl)-2-phenylcyclohexyl]acrylate (10**):** Methyl (triphenylphosphoranylidene)acetate (200.6 mg, 0.60 mmol) was added in one portion to a stirred solution of **3a** (33.4 mg, 0.10 mmol) in anhydrous dichloromethane (1.0 mL) at 0 °C. The reaction mixture was allowed to warm slowly to rt. After stirring for 2 h, the solvent was then evaporated and the crude product was purified by column chromatography using 75:25 hexane/EtOAc to give product **10** (28.5 mg, 73% yield).

Dimethyl (2*E*,2'*E*)-3,3'-[(1*R*,2*R*,3*S*,4*R*)-4-(2-oxo-2-phenylethyl)-2-phenylcyclohexane-1,3-diyl]diacrylate (11**):** Methyl (triphenylphosphoranylidene)acetate (267.4 mg, 0.80 mmol) was added in one portion to a stirred solution of **3a** (33.4 mg,

0.10 mmol) in anhydrous dichloromethane (1.0 mL) at 0 °C. The reaction mixture was allowed to warm slowly to rt. After stirring for 48 h, the solvent was then evaporated and the crude product was purified by column chromatography using 75:25 hexane/EtOAc to give product **11** (32.2 mg, 72% yield).

(1*S*,2*R*,3*R*,4*R*)-4-(2-Oxo-2-phenylethyl)-2-phenylcyclohexane-1,3-dicarbaldehyde (3a**):** Colorless liquid, 29.8 mg, 89% yield; ¹H NMR (500 MHz, CDCl₃) δ 9.45 (d, *J* = 2.7 Hz, 1H), 9.42 (d, *J* = 3.7 Hz, 1H), 7.98 – 7.86 (m, 2H), 7.62 – 7.54 (m, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.37 – 7.17 (m, 5H), 3.21 (t, *J* = 11.0 Hz, 1H), 3.10 (dd, *J* = 17.1, 3.4 Hz, 1H), 2.86 (dd, *J* = 17.0, 7.3 Hz, 1H), 2.73 (tt, *J* = 12.0, 3.2 Hz, 1H), 2.58 (dd, *J* = 10.2, 3.9 Hz, 2H), 2.17 (dd, *J* = 13.3, 3.4 Hz, 1H), 2.04 (dd, *J* = 13.6, 3.5 Hz, 1H), 1.60 (qd, *J* = 13.3, 3.6 Hz, 1H), 1.43 – 1.30 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 203.5, 202.7, 198.5, 139.3, 136.8, 133.3, 129.2, 128.7, 128.0, 128.0, 127.8, 60.6, 54.6, 45.5, 42.7, 32.9, 30.5, 25.9. *v*_{max} (neat, cm⁻¹): 2941, 1701, 1597, 1493, 1105, 1001. HRMS (ESI): *m/z* calcd for C₂₂H₂₃O₃ ([M+H]⁺): 335.1642; Found 335.1638. Enantiomeric excess of **3a** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (70:30 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: *t*_R = 18.5 min, minor enantiomer: *t*_R = 21.8 min.

(1*S*,2*R*,3*R*,4*R*)-2-(4-Methoxyphenyl)-4-(2-oxo-2-phenylethyl)-cyclohexane-1,3-dicarbaldehyde (3b**):** Colorless liquid, 18.2 mg, 50% yield; ¹H NMR (500 MHz, CDCl₃) δ 9.46 (d, *J* = 2.8 Hz, 1H), 9.41 (d, *J* = 3.6 Hz, 1H), 7.99 – 7.87 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 3.79 (s, 3H), 3.16 (d, *J* = 11.0 Hz, 1H), 3.09 (dd, *J* = 17.2, 3.3 Hz, 1H), 2.85 (dd, *J* = 17.1, 7.2 Hz, 1H), 2.70 – 2.61 (m, 1H), 2.59 – 2.49 (m, 2H), 2.16 (dd, *J* = 13.3, 3.4 Hz, 1H), 2.02 (dd, *J* = 13.6, 3.6 Hz, 1H), 1.61 (d, *J* = 3.6 Hz, 1H), 1.35 (dd, *J* = 11.3, 3.5 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 203.7, 203.0, 198.5, 158.9, 136.8, 133.3, 131.2, 128.9, 128.7, 128.0, 114.6, 60.8, 55.2, 54.8, 44.7, 42.7, 32.9, 30.5, 26.0. *v*_{max} (neat, cm⁻¹): 2851, 1716, 1681, 1447, 1179, 1001. HRMS (ESI): *m/z* calcd for C₂₃H₂₅O₄ ([M+H]⁺): 365.1747; Found 365.1737. Enantiomeric excess of **3b** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (70:30 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: *t*_R = 34.4 min, minor enantiomer: *t*_R = 37.5 min.

(1*S*,2*R*,3*R*,4*R*)-4-(2-Oxo-2-phenylethyl)-2-(*p*-tolyl)cyclohexane-1,3-dicarbaldehyde (3c**):** Colorless liquid, 26.5 mg, 76% yield; ¹H NMR (500 MHz, CDCl₃) δ 9.45 (d, *J* = 2.7 Hz, 1H), 9.41 (d, *J* = 3.4 Hz, 1H), 8.03 – 7.82 (m, 2H), 7.59 (s, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.12 (d, *J* = 3.1 Hz, 4H), 3.21 – 3.03 (m, 2H), 2.85 (dd, *J* = 17.0, 7.2 Hz, 1H), 2.69 (tt, *J* = 11.9, 3.3 Hz, 1H), 2.62 – 2.48 (m, 2H), 2.31 (s, 3H), 2.16 (dd, *J* = 13.6, 3.3 Hz, 1H), 2.02 (dq, *J* = 13.6, 3.5 Hz, 1H), 1.64 – 1.55 (m, 1H), 1.35 (dd, *J* = 11.4, 3.8 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 203.6, 203.0, 198.5, 137.4, 136.8, 136.1, 133.3, 129.9, 128.7, 128.0, 127.8, 60.6, 54.7, 45.1, 42.7, 32.9, 30.5, 25.9, 21.0. *v*_{max} (neat, cm⁻¹): 2923, 1717, 1682, 1447, 1180, 1002. HRMS (ESI): *m/z* calcd for C₂₃H₂₅O₃ ([M+H]⁺): 349.1798; Found 349.1794. Enantiomeric excess of **3c** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (70:30 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: *t*_R = 18.0 min, minor enantiomer: *t*_R = 22.3 min.

(1S,2R,3R,4R)-2-(4-Fluorophenyl)-4-(2-oxo-2-phenylethyl)-cyclohexane-1,3-dicarbaldehyde (3d): Colorless liquid, 24.7 mg, 70% yield; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.46 (d, $J = 2.6$ Hz, 1H), 9.41 (d, $J = 3.7$ Hz, 1H), 7.93 (d, $J = 7.7$ Hz, 2H), 7.58 (d, $J = 7.4$ Hz, 1H), 7.48 (t, $J = 7.6$ Hz, 2H), 7.21 (dd, $J = 8.4, 5.2$ Hz, 2H), 7.02 (t, $J = 8.4$ Hz, 2H), 3.24 (t, $J = 10.9$ Hz, 1H), 3.09 (dd, $J = 17.2, 3.5$ Hz, 1H), 2.87 (dd, $J = 17.2, 6.7$ Hz, 1H), 2.69 (tt, $J = 12.0, 3.2$ Hz, 1H), 2.55 (t, $J = 5.1$ Hz, 2H), 2.17 (dt, $J = 10.9, 3.5$ Hz, 1H), 2.09 – 2.00 (m, 1H), 1.62 – 1.55 (m, 1H), 1.37 (dd, $J = 11.3, 3.5$ Hz, 1H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 203.2, 202.3, 198.4, 162.0 (d, $J_{\text{C-F}} = 247.0$ Hz), 136.8, 135.2 (d, $J_{\text{C-F}} = 4.0$ Hz), 133.4, 129.5 (d, $J_{\text{C-F}} = 8.8$ Hz), 128.7, 128.0, 116.2 (d, $J_{\text{C-F}} = 27.7$ Hz), 60.7, 54.8, 44.4, 42.8, 32.9, 30.5, 26.0. ν_{max} (neat, cm^{-1}): 2952, 1703, 1584, 1448, 1161, 1070. HRMS (ESI): m/z calcd for $\text{C}_{22}\text{H}_{22}\text{FO}_3$ ($[\text{M}+\text{H}]^+$): 353.1547; Found 353.1546. Enantiomeric excess of **3d** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (70:30 hexanes/*i*-PrOH at 1.0 mL/min, $\lambda = 254$ nm), major enantiomer: $t_{\text{R}} = 18.6$ min, minor enantiomer: $t_{\text{R}} = 22.2$ min.

(1S,2R,3R,4R)-2-(4-Chlorophenyl)-4-(2-oxo-2-phenylethyl)-cyclohexane-1,3-dicarbaldehyde (3e): Colorless liquid, 24.0 mg, 65% yield; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.46 (d, $J = 2.5$ Hz, 1H), 9.41 (d, $J = 3.6$ Hz, 1H), 8.07 – 7.82 (m, 2H), 7.59 (t, $J = 7.4$ Hz, 1H), 7.49 (d, $J = 7.7$ Hz, 2H), 7.34 – 7.24 (m, 2H), 7.17 (d, $J = 8.3$ Hz, 2H), 3.23 (t, $J = 11.0$ Hz, 1H), 3.09 (dd, $J = 17.2, 3.4$ Hz, 1H), 2.88 (dd, $J = 17.2, 7.1$ Hz, 1H), 2.76 – 2.64 (m, 1H), 2.55 (td, $J = 7.5, 4.0$ Hz, 2H), 2.18 (dd, $J = 13.3, 3.3$ Hz, 1H), 2.07 (dd, $J = 13.6, 3.5$ Hz, 1H), 1.61 (d, $J = 9.4$ Hz, 1H), 1.38 (d, $J = 3.3$ Hz, 1H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 203.1, 202.1, 198.3, 138.0, 136.7, 133.5, 133.4, 129.4, 129.3, 128.7, 128.0, 60.5, 54.7, 44.5, 42.5, 32.9, 30.5, 25.9. ν_{max} (neat, cm^{-1}): 2922, 1716, 1682, 1596, 1491, 1265, 1001. HRMS (ESI): m/z calcd for $\text{C}_{22}\text{H}_{22}\text{ClO}_3$ ($[\text{M}+\text{H}]^+$): 369.1252; Found 369.1246. Enantiomeric excess of **3e** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (70:30 hexanes/*i*-PrOH at 1.0 mL/min, $\lambda = 254$ nm), major enantiomer: $t_{\text{R}} = 14.7$ min, minor enantiomer: $t_{\text{R}} = 18.3$ min.

(1S,2R,3R,4R)-2-(4-Bromophenyl)-4-(2-oxo-2-phenylethyl)-cyclohexane-1,3-dicarbaldehyde (3f): Colorless liquid, 29.8 mg, 72% yield; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.46 (d, $J = 2.5$ Hz, 1H), 9.41 (d, $J = 3.5$ Hz, 1H), 7.99 – 7.86 (m, 2H), 7.59 (s, 1H), 7.47 (dd, $J = 16.8, 8.1$ Hz, 4H), 7.12 (d, $J = 8.1$ Hz, 2H), 3.22 (t, $J = 11.1$ Hz, 1H), 3.07 (d, $J = 3.5$ Hz, 1H), 2.89 (s, 1H), 2.70 (s, 1H), 2.60 – 2.51 (m, 2H), 2.18 (dd, $J = 13.3, 3.4$ Hz, 1H), 2.06 (s, 1H), 1.60 (s, 1H), 1.44 – 1.31 (m, 1H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 203.1, 202.1, 198.3, 138.5, 136.7, 133.4, 132.3, 129.7, 128.7, 128.0, 121.6, 60.4, 54.6, 44.6, 42.5, 32.9, 30.5, 25.9. ν_{max} (neat, cm^{-1}): 2921, 1716, 1682, 1447, 1221, 1009. HRMS (ESI): m/z calcd for $\text{C}_{22}\text{H}_{22}\text{BrO}_3$ ($[\text{M}+\text{H}]^+$): 413.0747; Found 413.0740. Enantiomeric excess of **3f** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (70:30 hexanes/*i*-PrOH at 1.0 mL/min, $\lambda = 254$ nm), major enantiomer: $t_{\text{R}} = 16.2$ min, minor enantiomer: $t_{\text{R}} = 20.2$ min.

4-[(1R,2R,3R,6S)-2,6-Diformyl-3-(2-oxo-2-phenylethyl)-cyclohexyl]benzotrile (3g): Colorless liquid, 20.2 mg, 56% yield; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.47 (d, $J = 2.2$ Hz, 1H), 9.41 (d, $J = 3.4$ Hz, 1H), 7.98 – 7.85 (m, 2H), 7.62 (t, $J = 8.8$ Hz, 3H),

7.49 (t, $J = 7.6$ Hz, 2H), 7.37 (d, $J = 8.0$ Hz, 2H), 3.34 (t, $J = 11.2$ Hz, 1H), 3.09 (dd, $J = 17.4, 3.3$ Hz, 1H), 2.97 – 2.86 (m, 1H), 2.83 – 2.71 (m, 1H), 2.64 – 2.47 (m, 2H), 2.18 (ddd, $J = 26.7, 13.4, 3.4$ Hz, 2H), 1.53 (d, $J = 3.4$ Hz, 1H), 1.42 (dd, $J = 11.6, 3.3$ Hz, 1H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 202.5, 201.2, 198.1, 145.3, 136.7, 133.5, 132.9, 129.0, 128.7, 128.0, 118.3, 111.7, 60.2, 54.5, 44.7, 42.4, 32.9, 30.5, 25.9. ν_{max} (neat, cm^{-1}): 2927, 1716, 1683, 1275, 1116, 1001. HRMS (ESI): m/z calcd for $\text{C}_{23}\text{H}_{22}\text{NO}_3$ ($[\text{M}+\text{H}]^+$): 360.1594; Found 360.1593. Enantiomeric excess of **3g** was determined by chiral stationary phase HPLC analysis using a ChiralPak ID column (60:40 hexanes/*i*-PrOH at 1.0 mL/min, $\lambda = 254$ nm), major enantiomer: $t_{\text{R}} = 34.6$ min, minor enantiomer: $t_{\text{R}} = 48.9$ min.

(1S,2R,3R,4R)-4-[2-(4-Methoxyphenyl)-2-oxoethyl]-2-phenyl-cyclohexane-1,3-dicarbaldehyde (3h): Colorless liquid, 24.8 mg, 68% yield; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.45 (d, $J = 2.6$ Hz, 1H), 9.41 (d, $J = 4.0$ Hz, 1H), 7.92 (d, $J = 8.9$ Hz, 2H), 7.33 (dd, $J = 8.6, 6.6$ Hz, 2H), 7.28 – 7.18 (m, 3H), 6.95 (d, $J = 8.9$ Hz, 2H), 3.89 (s, 3H), 3.20 (t, $J = 11.1$ Hz, 1H), 3.04 (dd, $J = 16.7, 3.6$ Hz, 1H), 2.86 – 2.67 (m, 2H), 2.57 (dd, $J = 11.0, 4.2$ Hz, 2H), 2.19 – 2.10 (m, 1H), 2.03 (dd, $J = 13.6, 3.5$ Hz, 1H), 1.59 (dd, $J = 12.7, 3.6$ Hz, 1H), 1.36 (dd, $J = 11.1, 3.3$ Hz, 1H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 203.6, 202.8, 197.0, 163.7, 139.3, 130.4, 129.9, 129.2, 128.0, 127.8, 113.8, 60.6, 55.5, 54.7, 45.5, 42.3, 33.1, 30.5, 25.9. ν_{max} (neat, cm^{-1}): 2933, 1720, 1673, 1599, 1263, 1029. HRMS (ESI): m/z calcd for $\text{C}_{23}\text{H}_{25}\text{O}_4$ ($[\text{M}+\text{H}]^+$): 365.1747; Found 365.1741. Enantiomeric excess of **3h** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (60:40 hexanes/*i*-PrOH at 1.0 mL/min, $\lambda = 254$ nm), major enantiomer: $t_{\text{R}} = 25.2$ min, minor enantiomer: $t_{\text{R}} = 28.9$ min.

(1S,2R,3R,4R)-4-[2-Oxo-2-(*p*-tolyl)ethyl]-2-phenylcyclohexane-1,3-dicarbaldehyde (3i): Colorless liquid, 25.1 mg, 72% yield; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.45 (d, $J = 2.7$ Hz, 1H), 9.41 (d, $J = 3.8$ Hz, 1H), 7.84 (d, $J = 8.0$ Hz, 2H), 7.32 (d, $J = 7.4$ Hz, 2H), 7.30 – 7.22 (m, 5H), 3.21 (t, $J = 11.0$ Hz, 1H), 3.07 (dd, $J = 17.0, 3.5$ Hz, 1H), 2.83 (dd, $J = 16.9, 7.4$ Hz, 1H), 2.76 – 2.66 (m, 1H), 2.57 (dd, $J = 11.0, 4.5$ Hz, 2H), 2.43 (s, 3H), 2.16 (dd, $J = 13.4, 3.4$ Hz, 1H), 2.07 – 1.97 (m, 1H), 1.60 (dd, $J = 12.8, 3.7$ Hz, 1H), 1.37 (td, $J = 12.3, 11.2, 3.3$ Hz, 1H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 203.5, 202.8, 198.1, 144.2, 139.3, 134.4, 129.3, 129.2, 128.2, 128.0, 127.8, 60.6, 54.7, 45.5, 42.5, 33.0, 30.5, 25.9, 21.7. ν_{max} (neat, cm^{-1}): 2921, 1716, 1682, 1494, 1274, 1120, 1017. HRMS (ESI): m/z calcd for $\text{C}_{23}\text{H}_{25}\text{O}_3$ ($[\text{M}+\text{H}]^+$): 349.1798; Found 349.1794. Enantiomeric excess of **3i** was determined by chiral stationary phase HPLC analysis using a ChiralPak ID column (60:40 hexanes/*i*-PrOH at 1.0 mL/min, $\lambda = 254$ nm), major enantiomer: $t_{\text{R}} = 22.3$ min, minor enantiomer: $t_{\text{R}} = 32.2$ min.

(1S,2R,3R,4R)-4-[2-(4-Fluorophenyl)-2-oxoethyl]-2-phenyl-cyclohexane-1,3-dicarbaldehyde (3j): Colorless liquid, 24.0 mg, 68% yield; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.45 (d, $J = 2.6$ Hz, 1H), 9.40 (d, $J = 3.7$ Hz, 1H), 7.97 (dd, $J = 8.6, 5.4$ Hz, 2H), 7.33 (t, $J = 7.5$ Hz, 2H), 7.28 – 7.22 (m, 3H), 7.15 (t, $J = 8.5$ Hz, 2H), 3.20 (t, $J = 11.1$ Hz, 1H), 3.08 (dd, $J = 17.1, 3.5$ Hz, 1H), 2.86 – 2.68 (m, 2H), 2.62 – 2.52 (m, 2H), 2.16 (dd, $J = 13.3, 3.4$ Hz, 1H), 2.04 (dd, $J = 13.6, 3.5$ Hz, 1H), 1.64 – 1.57 (m, 1H), 1.45 – 1.30 (m, 1H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 203.6, 202.7, 196.8, 165.8 (d, $J_{\text{C-F}} = 255.7$ Hz), 139.2, 133.2 (d, $J_{\text{C-F}} = 3.8$ Hz), 130.8, 130.7, 129.3,

127.8 (d, $J_{CF} = 15.1$ Hz), 115.7 (d, $J_{CF} = 22.7$ Hz), 60.5, 54.6, 45.5, 42.6, 32.9, 30.5, 25.9. ν_{max} (neat, cm^{-1}): 2931, 1703, 1596, 1228, 1157, 1000. HRMS (ESI): m/z calcd for $C_{22}H_{22}FO_3$ ($[M+H]^+$): 353.1547; Found 353.1546. Enantiomeric excess of **3j** was determined by chiral stationary phase HPLC analysis using a ChiralPak ID column (70:30 hexanes/*i*-PrOH at 1.0 mL/min, $\lambda = 254$ nm), major enantiomer: $t_R = 21.2$ min, minor enantiomer: $t_R = 31.0$ min.

(1S,2R,3R,4R)-4-[2-(4-Chlorophenyl)-2-oxoethyl]-2-phenylcyclohexane-1,3-dicarbaldehyde (3k): Colorless liquid, 25.8 mg, 70% yield; 1H NMR (500 MHz, $CDCl_3$) δ 9.45 (d, $J = 2.6$ Hz, 1H), 9.40 (d, $J = 3.7$ Hz, 1H), 7.88 (d, $J = 8.3$ Hz, 2H), 7.45 (d, $J = 8.2$ Hz, 2H), 7.33 (t, $J = 7.5$ Hz, 2H), 7.27 – 7.18 (m, 3H), 3.20 (t, $J = 11.1$ Hz, 1H), 3.08 (dd, $J = 17.1$, 3.6 Hz, 1H), 2.77 (ddd, $J = 38.0$, 14.5, 8.0 Hz, 2H), 2.57 (dd, $J = 10.3$, 4.0 Hz, 2H), 2.15 (dd, $J = 13.3$, 3.4 Hz, 1H), 2.05 (dd, $J = 13.6$, 3.5 Hz, 1H), 1.60 (dd, $J = 12.9$, 3.7 Hz, 1H), 1.46 – 1.31 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.6, 202.7, 197.3, 139.8, 139.2, 135.1, 129.5, 129.28, 129.0, 127.9, 127.8, 60.5, 54.6, 45.5, 42.7, 32.8, 30.5, 25.9. ν_{max} (neat, cm^{-1}): 2932, 1721, 1683, 1400, 1275, 1092. HRMS (ESI): m/z calcd for $C_{22}H_{22}ClO_3$ ($[M+H]^+$): 369.1252; Found 369.1246. Enantiomeric excess of **3k** was determined by chiral stationary phase HPLC analysis using a ChiralPak ID column (70:30 hexanes/*i*-PrOH at 1.0 mL/min, $\lambda = 254$ nm), major enantiomer: $t_R = 25.3$ min, minor enantiomer: $t_R = 38.0$ min.

(1S,2R,3R,4R)-4-[2-(4-Bromophenyl)-2-oxoethyl]-2-phenylcyclohexane-1,3-dicarbaldehyde (3l): Colorless liquid, 25.2 mg, 61% yield; 1H NMR (500 MHz, $CDCl_3$) δ 9.45 (d, $J = 2.5$ Hz, 1H), 9.39 (d, $J = 3.6$ Hz, 1H), 7.80 (d, $J = 8.2$ Hz, 2H), 7.62 (d, $J = 8.1$ Hz, 2H), 7.34 – 7.22 (m, 5H), 3.20 (t, $J = 11.0$ Hz, 1H), 3.07 (dd, $J = 17.1$, 3.6 Hz, 1H), 2.76 (ddd, $J = 35.1$, 14.5, 7.9 Hz, 2H), 2.56 (dt, $J = 7.3$, 3.8 Hz, 2H), 2.14 (dt, $J = 13.0$, 3.5 Hz, 1H), 2.04 (dq, $J = 13.8$, 3.6 Hz, 1H), 1.61 – 1.55 (m, 1H), 1.41 – 1.31 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.6, 202.7, 197.7, 139.2, 135.5, 132.0, 129.6, 129.3, 128.6, 127.9, 127.8, 60.5, 54.6, 45.5, 42.7, 32.8, 30.5, 25.9. ν_{max} (neat, cm^{-1}): 2931, 1702, 1690, 1265, 1172, 1008. HRMS (ESI): m/z calcd for $C_{22}H_{22}BrO_3$ ($[M+H]^+$): 413.0747; Found 413.0744. Enantiomeric excess of **3l** was determined by chiral stationary phase HPLC analysis using a ChiralPak ID column (80:20 hexanes/*i*-PrOH at 1.0 mL/min, $\lambda = 254$ nm), major enantiomer: $t_R = 36.5$ min, minor enantiomer: $t_R = 49.2$ min.

(1S,2R,3R,4R)-4-[2-(3-Bromophenyl)-2-oxoethyl]-2-phenylcyclohexane-1,3-dicarbaldehyde (3m): Colorless liquid, 28.1 mg, 68% yield; 1H NMR (500 MHz, $CDCl_3$) δ 9.46 (d, $J = 2.6$ Hz, 1H), 9.40 (d, $J = 3.8$ Hz, 1H), 8.07 (t, $J = 1.9$ Hz, 1H), 7.86 (dt, $J = 7.7$, 1.3 Hz, 1H), 7.71 (ddd, $J = 8.0$, 2.0, 1.0 Hz, 1H), 7.35 (dt, $J = 15.3$, 7.6 Hz, 3H), 7.26 – 7.22 (m, 3H), 3.21 (t, $J = 11.2$ Hz, 1H), 3.08 (dd, $J = 17.3$, 3.7 Hz, 1H), 2.82 (dd, $J = 17.2$, 7.2 Hz, 1H), 2.77 – 2.67 (m, 1H), 2.59 – 2.53 (m, 2H), 2.15 (dd, $J = 13.2$, 3.4 Hz, 1H), 2.08 – 2.00 (m, 1H), 1.63 – 1.58 (m, 1H), 1.42 – 1.31 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.5, 202.6, 197.1, 139.2, 138.5, 136.2, 131.1, 130.3, 129.3, 128.0, 127.8, 126.6, 123.1, 60.4, 54.6, 45.5, 42.8, 32.8, 30.5, 25.9. ν_{max} (neat, cm^{-1}): 2951, 1756, 1685, 1270, 1195, 1005. HRMS (ESI): m/z calcd for $C_{22}H_{21}BrO_3$ ($[M+H]^+$): 413.0747; Found 413.0749. Enantiomeric excess of **3m** was determined by chiral stationary phase HPLC analysis

using a ChiralPak ID column (70:30 hexanes/*i*-PrOH at 1.0 mL/min, $\lambda = 254$ nm), major enantiomer: $t_R = 25.4$ min, minor enantiomer: $t_R = 44.3$ min.

Methyl (E)-3-[(1R,2R,3R,4R)-3-formyl-4-(2-oxo-2-phenylethyl)-2-phenylcyclohexyl]acrylate (10): Colorless liquid, 28.5 mg, 73% yield; 1H NMR (500 MHz, $CDCl_3$) δ 9.36 (d, $J = 3.9$ Hz, 1H), 8.00 – 7.84 (m, 2H), 7.62 – 7.54 (m, 1H), 7.48 (dd, $J = 8.4$, 7.1 Hz, 2H), 7.31 – 7.27 (m, 2H), 7.23 – 7.17 (m, 1H), 7.15 – 7.09 (m, 2H), 6.64 (dd, $J = 15.7$, 8.3 Hz, 1H), 5.56 (dd, $J = 15.8$, 1.0 Hz, 1H), 3.63 (s, 3H), 3.10 (dd, $J = 17.1$, 3.4 Hz, 1H), 2.87 – 2.74 (m, 2H), 2.63 – 2.44 (m, 3H), 2.11 (dd, $J = 13.3$, 3.3 Hz, 1H), 1.93 (dd, $J = 13.5$, 3.5 Hz, 1H), 1.61 – 1.50 (m, 1H), 1.42 – 1.31 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.7, 198.7, 166.6, 150.4, 140.0, 137.0, 133.2, 129.0, 128.6, 128.1, 127.9, 127.4, 121.3, 61.0, 51.4, 49.7, 45.7, 42.8, 33.1, 31.3, 31.0. ν_{max} (neat, cm^{-1}): 2917, 1718, 1679, 1560, 1270, 1150. HRMS (ESI): m/z calcd for $C_{25}H_{27}O_4$ ($[M+H]^+$): 391.1904; Found 391.1902. Enantiomeric excess of **10** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (70:30 hexanes/*i*-PrOH at 1.0 mL/min, $\lambda = 254$ nm), major enantiomer: $t_R = 19.7$ min, minor enantiomer: $t_R = 31.3$ min.

Dimethyl (2E,2'E)-3,3'-[(1R,2R,3S,4R)-4-(2-oxo-2-phenylethyl)-2-phenylcyclohexane-1,3-diyl]diacrylate (11): Colorless liquid, 32.2 mg, 72% yield, 1H NMR (500 MHz, $CDCl_3$) δ 7.94 – 7.87 (m, 2H), 7.58 (t, $J = 7.4$ Hz, 1H), 7.47 (dd, $J = 8.3$, 7.1 Hz, 2H), 7.23 (t, $J = 7.5$ Hz, 2H), 7.17 – 7.10 (m, 1H), 7.02 (d, $J = 7.4$ Hz, 2H), 6.62 (dd, $J = 15.7$, 7.9 Hz, 1H), 6.53 (dd, $J = 15.7$, 9.9 Hz, 1H), 5.54 (dd, $J = 15.7$, 0.9 Hz, 1H), 5.35 (d, $J = 15.7$ Hz, 1H), 3.62 (s, 3H), 3.57 (s, 3H), 3.06 (dd, $J = 16.6$, 3.6 Hz, 1H), 2.80 – 2.74 (m, 1H), 2.55 – 2.40 (m, 2H), 2.39 – 2.21 (m, 2H), 2.08 (dd, $J = 13.3$, 3.5 Hz, 1H), 1.91 (dd, $J = 13.4$, 3.4 Hz, 1H), 1.60 – 1.52 (m, 1H), 1.40 – 1.31 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.2, 166.8, 166.0, 151.3, 149.7, 141.6, 137.2, 133.1, 128.6, 128.5, 128.0, 126.8, 123.2, 120.7, 53.4, 52.7, 51.3, 45.9, 43.3, 37.5, 31.4, 31.2. ν_{max} (neat, cm^{-1}): 2918, 1712, 1690, 1478, 1270, 1119, 1009. HRMS (ESI): m/z calcd for $C_{28}H_{31}O_5$ ($[M+H]^+$): 447.2166; Found 447.2168. Enantiomeric excess of **11** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (70:30 hexanes/*i*-PrOH at 1.0 mL/min, $\lambda = 254$ nm), major enantiomer: $t_R = 25.4$ min, minor enantiomer: $t_R = 43.4$ min.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors thank the Welch Foundation (Grant No. AX-1593) and the National Science Foundation (Grant No. CHE-1664278) for the financial support of this project. We thank Dr. Daniel Wherritt for help with the 2-D COSY experiments.

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